

In re Application of:
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Remarks

Claim 1 has been amended. Claims 21-27 have been canceled. Subsequent to the entry of the present amendment, claims 1-20 and 28-29 are pending and at issue. Reconsideration of the application is respectfully requested in view of the following remarks.

Claim Rejections – 35 USC § 112

The examiner has rejected claim 1 as being indefinite for failing to particularly point out and distinctly claim the invention and for being unclear as to what the active method steps to produce the recited particles are.

Claim 1 has been amended to recite

A method of forming fine particles of a substance, the method including the steps of:

- (i) providing an aqueous, non-gaseous fluid containing the substance;*
 - (ii) providing a dense gas including (a) an antisolvent and (b) a modifying agent which modifies the polarity of the antisolvent ;*
 - (iii) contacting the aqueous, non-gaseous with the dense gas to expand the fluid and thereby form the fine particles;*
- wherein the fine particles are formed upon contacting the aqueous, non-gaseous fluid and the dense gas.*

The examiner has suggested that the phrase “whereupon the fine particles of the substance are formed at the point of contact between the non-gaseous fluid and the dense gas” be added at the end of the claim. We disagree that the claim needs to be amended in this way. The particles form wherever the contact between the aqueous, non-gaseous fluid and the dense gas occurs, rather than at a specific point which we consider to be clear from the claim and the use of the phrase “the fine particles are formed upon contacting the aqueous, non-gaseous fluid and the dense gas”.

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Claim Rejections – 35 USC § 102

The examiner has rejected claims 21 to 24 and 27 as being anticipated by Debenedetti *et al.* (U.S. Patent No. 6,063,910).

Claims 21 to 24 and 27 (the product-by-process claims) have been canceled, rendering this rejection moot.

Claim Rejections – 35 USC § 103

The examiner has rejected claims 1 to 24 and 27 to 29 under 35 USC § 103 as being unpatentable over Debenedetti *et al.* in view of Merrified *et al.* (PCT Publication No. WO 00/37169). This rejection is moot regarding canceled claims 21-24 and 27. Applicants respectfully traverse the rejection as it applies to the pending claims 1-20, 28 and 29.

Claim 1 of the present application has been amended to recite:

A method of forming fine particles of a substance, the method including the steps of:

- (i) providing an aqueous, non-gaseous fluid containing the substance;*
 - (ii) providing a dense gas including (a) an antisolvent and (b) a modifying agent which modifies the polarity of the antisolvent ;*
 - (iii) contacting the aqueous, non-gaseous with the dense gas to expand the fluid and thereby form the fine particles;*
- wherein the fine particles are formed upon contacting the aqueous, non-gaseous fluid and the dense gas.*

As stated at [0047] of the present application, the method of the present invention has the advantage that the use of an aqueous non-gaseous fluid allows particles of the substance of interest to be produced with minimal risk of deactivation of the biological activity of the substance. The use of aqueous non-gaseous fluids is also advantageous in that such fluids are

much easier and cheaper to handle e.g.; from a safety perspective (i.e.; less solvent vapors and reduced flammability risk).

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation to modify a document or to combine the teachings of multiple documents. Second, there must be a reasonable expectation of success. Third, the prior art must teach or suggest all of the recited claim limitations. Of course, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure.

Motivation to combine documents

We submit that it is not at all obvious that one of ordinary skill in the art would be motivated to combine the disclosures of Debenedetti *et al.* and Merrified *et al.*

Debenedetti *et al.* relates to a process for the formation of microparticles (particularly protein microparticles) from a solution by forming a solution of the protein in a solvent and dissolving a supercritical anti solvent fluid in the solution at a controlled rate to expand the solution and precipitate the protein. It is stated at column 2, lines 36 to 40 that preferred solvents for the protein are non-aqueous solvents, including ethanol, dimethylsulfoxide, acetic acid, etc. The two examples in Debenedetti *et al.* involve the precipitation of catalase (Example 1) and insulin (Example 2) from a solution of ethanol (90%) and water (10%) – a non-aqueous solvent.

Merrified *et al.* describes a process and apparatus for the production of particles of a material in which a stream of a dispersion of the material in a solvent and a stream of a compressible fluid antisolvent substance are mixed under conditions such that the substance is in a in such a way that the substance is in a compressible fluid antisolvent state. The solvents suitable for the process are organic solvents (see page 6, lines 18 to 22) and the examples in Merrified involved

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the materials carbapenem dissolved in the organic solvent ethyl acetate (Example 1) and nabumetone dissolved in a mixture of the organic solvents methanol and acetone (Example 2).

Both Debenedetti *et al.* and Merrified *et al.*, therefore, use organic solvents in their processes.

We submit that there is no motivation in either Debenedetti *et al.* or Merrified *et al.* to modify either document or combine the documents as they both use organic solvents in their processes and there is no teaching or suggestion in either document that an aqueous solvent could be used in the processes.

Reasonable expectation of success

The Office Action states that “one of ordinary skill in the art would seek to exert a greater degree of control over the processes disclosed by Debenedetti *et al.* by the use of modifying agents in the supercritical anti-solvent, as taught by Merrified *et al.*”

We disagree. Particle precipitation processes involving dense gases (or supercritical fluids or compressible fluid antisolvents) are very sensitive to even minor changes to the process. It is very difficult to predict the likely result of making a change to such a process.

We consider that changing the process of Debenedetti *et al.* to include a modifier as taught by Merrified *et al.*, is not obvious to one of ordinary skill in the art and given the unpredictability of the result, would not be likely to be the action of someone who “seek[s] to exert a greater degree of control over the processes disclosed by Debenedetti” *et al.*.

Further, in relation to amended claim 1, set out above, we submit that it is not a matter of routine to replace a non-aqueous solvent as used in the Debenedetti *et al.* process with an aqueous solvent. The change from use of a non-aqueous fluid to an aqueous non-gaseous fluid is a

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substantial change which may lead to any number of unpredictable changes to the outcome of the process, including dramatic phase shifts in the system which affect fluid dynamics and the entire particle nucleation process at the micro level. Thus, we submit that the skilled person would not be motivated to modify the Debenedetti *et al.* process by using an aqueous and have a reasonable expectation of success.

Prior art must teach/suggest all of the recited claim limitations

In relation to Debenedetti *et al.*, we submit that the process described in the document does not teach or suggest all of the features recited in claim 1 of the present application. As outlined above, Debenedetti *et al.* provides no teaching or suggestion that the solvent used in the process could be other than an organic solvent, as is required by claim 1 of the present application. We direct the Examiner to our discussion above, under the heading "Motivation to combine documents".

In relation to Merrified *et al.*, we submit that the process described in the document does not teach or suggest all of the features recited in claim 1 of the present application. As outlined above, Merrified *et al.* provides no teaching or suggestion that the solvent used in the process could be other than an organic solvent, as is required by claim 1 of the present application. We direct the Examiner to our discussion above, under the heading "Motivation to combine documents".

We therefore submit that claim 1 of the present application is not obvious in light of Debenedetti *et al.* in view of Manning *et al.* for at least the reasons stated above. Accordingly, for at least the reasons stated above, Applicants respectfully request that the rejection of claims 1-20, 28 and 29 under 35 USC §103 be withdrawn.

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Conclusion

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

Check number 585619 in the amount of \$510.00 is enclosed as payment for the three-month Extension of Time fee (small entity). Applicants do not believe any additional fees are due in connection with this Response. However, the Commissioner is hereby authorized to charge any fees that are required, or credit any overpayments to Deposit Account No. 07-1896 referencing the above-identified attorney docket number. A copy of the Transmittal Sheet is enclosed.

Respectfully submitted,

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